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Analysis of potentially modifiable risk factors of multiple sclerosis

Analiza potencjalnie modyfikowalnych czynników ryzyka stwardnienia rozsianego

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Abstract

Multiple sclerosis, also known as sclerosis multiplex, is a chronic autoimmune disease of the central nervous system that occurs in over 2.9 millions individuals worldwide, most commonly in young to middle-aged adults, with a greater prevalence in females than males and in higher latitudes. There are different types of multiple sclerosis, varying in the presence and frequency of relapses and remissions. Various risk factors for the disorder have been identified as well – both modifiable and unmodifiable. Although many remain elusive, there are multiple theories regarding them. The causes of multiple sclerosis are yet to be established but a family history of the disease may increase the risk, and also environmental factors are believed to play a role. This paper focuses on the potentially modifiable factors. The most common theory seems to postulate an association between the disorder and viral infections, especially in individuals with Epstein–Barr virus infection, but also human herpesvirus 6, varicella-zoster virus, cytomegalovirus, or John Cunningham virus. Other risk factors include vitamin D insufficiency, or even its low levels, as multiple sclerosis is more frequent in higher latitudes. Obesity, especially during childhood and adolescence, can also be a risk factor of so-called paediatric-onset multiple sclerosis. Obesity is also linked to a higher severity of multiple sclerosis in adults. Risk factors associated with a potentially lower risk, or even some positive effects, include alcohol and caffeine consumption, as well as smoking and oral tobacco use.

Keywords: obesity, vitamin D, herpes viruses, multiple sclerosis

Streszczenie

Stwardnienie rozsiane to przewlekła choroba autoimmunologiczna układu nerwowego, występująca u ponad 2,9 miliona osób na całym świecie, zwykle u młodych i dorosłych w średnim wieku, częściej u kobiet niż u mężczyzn i w wyższych szerokościach geograficznych. Istnieją różne typy stwardnienia rozsianego, różniące się obecnością i częstością występowania rzutów i remisji choroby. Wskazuje się również na wiele czynników ryzyka – zarówno modyfikowalnych, jak i niemodyfikowalnych. Choć wiele z nich nie zostało odkrytych, istnieją rozmaite teorie na ich temat. Przyczyny choroby nie są jeszcze znane, ale rodzinne występowanie może zwiększyć ryzyko zachorowania, ponadto uważa się, że czynniki środowiskowe odgrywają istotną rolę. Praca skupia się na tych potencjalnie modyfikowalnych czynnikach. Wydaje się, że najpopularniejsza teoria jest związana z zakażeniem wirusowym, zwłaszcza u osób zakażonych wirusem Epsteina–Barr, ale także ludzkim wirusem herpes 6, wirusem półpaśca, cytomegalowirusem lub wirusem Johna Cunninghama. Inne czynniki ryzyka obejmują niedobór witaminy D lub nawet jej niski poziom – stwierdzono, że stwardnienie rozsiane jest częstsze w wyższych szerokościach geograficznych. Otyłość, zwłaszcza w okresie dzieciństwa i adolescencji, może być czynnikiem ryzyka tzw. stwardnienia rozsianego u dzieci, jak również koreluje z większym nasileniem choroby u dorosłych. Czynniki ryzyka związane z potencjalnie niższym ryzykiem lub nawet z pewnymi pozytywnymi skutkami obejmują spożycie alkoholu i kofeiny oraz palenie tytoniu i używanie tytoniu doustnego.

Słowa kluczowe: otyłość, witamina D, wirusy herpes, stwardnienie rozsiane

INTRODUCTION

Multiple sclerosis (MS), also known under its Latin name *sclerosis multiplex* (SM), is a “chronic inflammatory demyelinating disease of the central nervous system (CNS), which gives rise to focal lesions in the gray and white matter and to diffuse neurodegeneration in the entire brain” (Lassmann, 2018). The presence of so-called plaques is a necessary factor in diagnosing MS. The level of demyelination correlates with the severity of the disease (Tarlinton et al., 2020). MS can occur at any age, but usually it affects young women, aged 20–40. It leads to disability, and it is considered as the leading cause of permanent disability in young adults (Kuhlmann and Antel, 2023). There are multiple genetic, environmental and socio-demographic theories about the risk factors associated with MS. Some of them, including genetics, are unmodifiable, while others, like viral infections or even the distance from the equator, could be regarded as modifiable (Alfredsson and Olsson, 2019).

The purpose of this paper was to analyse the available literature with the aim of:

1. outlining the possible modifiable risk factors of MS along with the level of their modifiability;
2. summarising the types of MS;
3. presenting the current epidemiology of MS.

MATERIALS AND METHODS

A literature search was performed to conduct this systematic review, using the PubMed and Google Scholar electronic databases. Only these two databases were used, as the aim was to focus on the most accessible journals and search engines. No article types were excluded. No particular language was set, but in the end works in English only were included. The keywords used were: “multiple sclerosis + epidemiology” OR “multiple sclerosis + viruses” OR “multiple sclerosis + Epstein–Barr virus” OR “multiple sclerosis + herpesviruses” OR “multiple sclerosis + cytomegalovirus” OR “multiple sclerosis + varicella zoster virus” OR “multiple sclerosis + HHV-6” OR “multiple sclerosis + John Cunningham virus” OR “multiple sclerosis + obesity” OR “multiple sclerosis + obesity + childhood” OR “multiple sclerosis + obesity + adolescent” OR “multiple sclerosis + environmental factors” OR “multiple sclerosis + vitamin D”. On Google Scholar, no particular language was chosen, the results were sorted by accuracy, and no specific type of publication was selected. The keywords used were the same as in the PubMed database. The works were published between 2016 and 2024.

Inclusion criteria:

1. publications on both multiple sclerosis and its risk factors.

Exclusion criteria:

1. articles focusing only on the included risk factors (e.g. viral infections) and not MS;

2. articles focusing only on paediatric-onset MS;
3. works focusing on autoimmune disorders other than MS.

No restrictions for age, sex, ethnicity etc. of individuals described in the papers were set.

RESULTS

In order to adapt to the requirements of the review to include no more than 30 references, a total of 30 articles and online sites were identified and synthesised in this review.

Epidemiology and statistics

Ward and Goldman (2022) concluded that in the recent decades the prevalence of MS had increased, and the costs of care for patients with MS had risen dramatically as well. Black, Asian, and Hispanic individuals might be at risk for more severe MS-related disability (Ward and Goldman, 2022).

In the US alone, 744,781 adults were identified with MS, 76% of them female, and the median age was determined as 45 to 54 years. Furthermore, 77% individuals were white, 10% black, and 7% Hispanic. The prevalence of MS was estimated at 375 per 100,000 population among white individuals, 298 per 100,000 among black individuals, and 161 per 100,000 among Hispanic individuals, while the correlation of prevalence with latitude was $r = 0.82$ (Hittle et al., 2023). In Poland, the total number of people suffering from MS is estimated as 51,000, with the prevalence 134 per 100,000 population (MS International Federation, 2024).

Overall, according to the National Multiple Sclerosis Society data, as of 2023, over 2.9 million people had MS worldwide (MS International Federation, 2024). The disorders occurs most commonly in young to middle-aged adults, more frequently in females than males, and it is more prevalent in higher latitudes (World Health Organization, 2023).

Viruses

Although no specific virus has been definitively proven as a causative factor of MS (Salehi et al., 2021), multiple viruses have been proposed as potential triggering factors, including the Epstein–Barr virus (EBV, HHV-4), human herpesvirus 6 (HHV-6), varicella-zoster virus (VZV, HHV-3), cytomegalovirus (CMV), John Cunningham virus (JCV), and also human endogenous retroviruses (Tarlinton et al., 2020). The cause is yet to be known, but several studies have indicated the possible mechanisms, such as direct toxicity, molecular mimicry, dual T cell receptor (TCR), bystander activation, and epitope spreading (Donati, 2020). It is also worth mentioning that after the infection the herpes viruses remain in the human body in a state of latency, which can cause a relapse of the infection, especially in immunocompromised individuals, e.g. patients with AIDS. Also, the general involvement of T cells, B cells and other various

cells of the immune system is currently seen as an established fact (Rice et al., 2021).

The most common theory regarding viral infection being a risk factor of MS is the one associated with the potentially oncogenic EBV. According to Bjornevik et al. (2022), EBV caused a 32-fold increase in the risk of MS after infection with EBV. Surprisingly, the authors of this study also concluded that the risk was not increased after infection with the similarly transmitted CMV, despite it being mentioned as a potential triggering factor in the previously quoted study by Tarlinton et al. (2020). Another assumption proposed by Bjornevik et al. (2022) was that EBV infection preceded both the onset of symptoms and the time of the first detectable pathological mechanisms underlying MS. HHV-6 is another virus that may possibly play a role in MS development. Salehi et al. (2021) focused on the role of EBV and HHV-6 in the acute phase of relapsing-remitting multiple sclerosis. They asserted that apart from the suspected role of viruses in the pathogenesis of MS, it is well known that natural killer (NK) and CD8⁺ T cells are vital mediators controlling viral infections. According to the authors, the composition of those cells was not associated with the viral load of either EBV or HHV-6, therefore it was assumed that other viral infections might be involved in altered NK and CD8⁺ T cell subpopulations. The researchers suggested that larger cohort studies needed to be performed (Salehi et al., 2021). In turn, Rice et al. (2021) devoted their whole study to VZV seropositivity, geographic heterogeneity, and MS. They found evidence for an association between having been infected with VZV and suffering from MS. Interestingly, this link was only proven in individuals from Asian countries, while in European countries no significant association was found (Rice et al., 2021). As mentioned, CMV infection seems to be controversial, or, in other words, “relatively unexplored” (Maple et al., 2020) in terms of being a risk factor of MS. Maple et al. (2020) in their UK study also agreed over the different response to CMV and EBV infection in individuals with MS compared to the controls, reporting that the EBV has a confirmed significant association with MS, while the CMV association requires further investigations. In their work, they concluded that CMV seroprevalence was significantly reduced in both groups of patients aged 40 or under and over 40 years. They proposed a thesis that ethnicity could also be a factor influencing the connection between the risk of MS and CMV seropositivity. Also, they pointed out that their study was related to the patients with MS remission who were not treated with steroids or disease-modifying drugs, but it was assumed that CMV modified the immune response and potentially reduced the severity of MS disease, as well as influenced the response to EBV infection (Maple et al., 2020). Zajkowska and Kułakowska (2018) in their review also assumed that CMV infection seemed to be an independent factor associated with the risk of MS, as the data is divergent – they presented both positive and negative correlations between these two factors, with the divergent data

related to the level of antibodies against CMV, the level of CMV-DNA, and MS itself. They also discussed the potentially protective influence of this virus in terms of MS occurrence (Zajkowska and Kułakowska, 2018). JCV infection seems to have the opposite effect, with Flores et al. (2021) reporting that the identification of single nucleotide mutants in the VP1 gene of JCV might be an early predictive marker to progressive multifocal leukoencephalopathy (PML) for efficient patient treatment with natalizumab (NTZ) and its follow-up. Sgarlata et al. (2022) also searched for the safest alternative for NTZ for patients with an increased JCV index to decrease the risk of the mentioned side effect of treatment. They suggested the use of B-cell profiled drugs in patients treated with NTZ with high anti-JCV antibodies, and re-starting NTZ therapy after reducing the JCV index below 1.50 or seroconversion to a negative status.

It is worth mentioning that in 2022 the National Institute of Allergy and Infectious Diseases, which is part of the National Institutes of Health, launched an early-stage clinical trial to evaluate an investigational preventative vaccine for EBV (National Institutes of Health, 2022).

Low vitamin D level, equator distance, and migration

The level of vitamin D and the distance of the place of residence from the Equator are related, as the number of sunny days correlates with the Equator distance. Exposure to the sun during pregnancy is believed to be the reason why most individuals suffering from MS were born during spring, and the fewest were born during autumn (Kiani, 2022). Curiously, this kind of seasonality is not observed near the Equator (Kiani, 2022). Also, as the World Health Organization (WHO) claims, the fact of MS occurring more commonly in higher latitudes may be due to sun exposure and vitamin D level (World Health Organization, 2023).

Interestingly, another theory is that migration before the age of 15 is associated with the risk of MS being similar to the risk in the target country, while migration after the age of 15 is associated with the risk of MS being similar to the risk in the home country (Munk et al., 2019).

Also, Munger et al. (2016) concluded that maternal vitamin D deficiency (defined as <30 nmol/L) during early pregnancy was associated with a nearly two-fold increase in the risk of MS in the offspring in comparison to women who were not vitamin D deficient.

Feige et al. (2020) claimed that hypovitaminosis D was linked to higher disease activity and possibly played a role in the long-term outcome. The authors tried to determine whether supplementation of cholecalciferol could decrease the risk of MS, but the data regarding the benefits of mentioned supplementation in patients with normal vitamin D levels remains to be set. Jacobs et al. (2020), in their randomised study of BMI and low vitamin D levels, strengthened the knowledge that vitamin D insufficiency remained

an independent causal risk factor for MS. The authors assumed that targeting this problem would not be a sufficient prevention strategy for MS, but it could have a more pronounced effect in early life among high-risk individuals (including those with a strong family history of MS). Ghareghani et al. (2023) claimed that both vitamin D and melatonin supplementation might improve MS symptoms, but the effects vary from patient to patient.

Obesity in childhood and adolescence

Obesity is defined as having a body mass index (BMI) of 30 kg/m² or higher. It is already known that obesity, or even high BMI in childhood and adolescence, increases the risk of multiple diseases, including autoimmune disorders like MS (Lutfullin et al., 2023). Mokry et al. (2016) estimated that obesity at the age of 18 was associated with more than a two-fold increase in the risk of MS. Not surprisingly, obesity probably not only increases the risk of MS itself, but is associated with a higher severity of the disease and poorer outcome. At the same time, successful treatment of obesity could improve MS clinical outcome, which makes it a clearly modifiable risk factor of MS (Lutfullin et al., 2023). Correale and Marrodan (2022) argued that this fact was correlated with the hormonal activity of the adipose tissue, which is capable of inducing chronic inflammatory changes, which is important, given that MS is chronic inflammatory disease. Harroud et al. (2021) performed a randomised study showing that also genetically predicted childhood obesity, as well as early adult obesity, was associated with MS susceptibility. It was proven that the persistence of obesity from childhood into adolescence also mediated a higher MS risk, remaining independent of pubertal timing (Harroud et al., 2021). Still, it was underlined that further investigations were necessary for better understanding of the mechanism. Alfredsson and Olsson (2019) found that obesity not only showed association with paediatric-onset MS (POMS, also referred to as paediatric MS, early-onset MS or juvenile MS), but also that the critical period seemed to be present during the adolescent period and not at 10 years of age. It is worth mentioning that POMS occurs in individuals aged less than 16 years. BMI before the age of 10 remains an independent causal risk factor for MS in the pathogenesis of MS (Jacobs et al., 2020).

It is important to highlight that POMS occurs as a relapsing-remitting type in 95–98% of cases (Brola and Steinborn, 2020).

Other lifestyle risk factors

There are some factors associated with a lower risk of MS. Alfredsson and Olsson (2019) concluded that the available data remained inconsistent and that certain risk factors were either associated with a lower risk, or had no impact at all. They included alcohol and coffee consumption, smoking, and oral tobacco use in this category (Alfredsson

and Olsson, 2019). Interestingly, according to Herden and Weissert's review (2018), caffeine has beneficial effects in MS. Also, there are multiple works investigating the effects of caffeine on cognitive functions in patients with MS, as well as attention and multiple sclerosis-related fatigue (Herden and Weissert, 2018). However, other studies (Ivashynka et al., 2022) excluded the possibility that coffee or tea intake could be associated with differences in the severity of MS.

CONCLUSIONS

The most important potentially modifiable MS risk factors include:

- EBV, HHV-6, VZV, CMV, and JCV infection;
- low vitamin D level;
- obesity in childhood and adolescence.

The actual impact of these risk factors requires further investigation. Also, there is still no evidence of how the mentioned factors can trigger the individuals' immune system to actually cause MS. Furthermore, most reported cases focus on the relapsing-remitting MS, as it is the most commonly occurring type of MS, though not the only one. The viral infection theory, especially the possible association between the EBV infection and SM, seems to be the source of the greatest interest among the scientists. Also, while JCV is associated with a higher risk of PML in patients treated with NTZ, CMV infection is sometimes mentioned as a factor potentially reducing the severity of MS, or even having a protecting influence, but this thesis needs further investigation. On the other hand, obesity is an obvious modifiable risk factor, also in childhood and adolescence. This is an important aspect because if individuals in the risk group are well-informed, they may implement prevention soon enough, which is especially important in the context of paediatric-onset MS. As MS tends to occur more often in higher latitudes, the association between vitamin D level and sun exposure and MS risk seems to be the best confirmed theory. Factors linked to a potentially lower risk of MS include alcohol and caffeine consumption, as well as smoking and oral tobacco use, but the actual impact of the latter remains undetermined.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study, collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: JL.

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